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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,146	05/05/2006	Shyam S. Mohapatra	USF T193XC1	9945

23557 7590 12/05/2008

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,146	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,45,46 and 51-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45,46 and 51-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was filed on 10/27/08. Claim 63 was added as requested.

Claims 42, 45, 46, and 51-63 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 45, 46, and 51-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting expression of Dengue virus (DV) genes within an isolated mammalian host cell by administering to the isolated host cell a vector that expresses siRNA that reduces expression of a target DV gene in the isolated host cell by RNA interference, does not reasonably provide enablement for inhibiting expression of Dengue virus (DV) genes within a mammalian animal host by administration to the animal host of a vector that expresses siRNA that reduces expression of a target DV gene in the host by RNA interference. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting expression of Dengue virus (DV) genes within a mammalian host by administration to the host of a vector that expresses siRNA that reduces expression of a target DV gene in the host by RNA interference.

This clearly requires delivery of the vector to cells that have been, or will be, infected by DV. The term "host" is interpreted as embracing both mammalian animals and isolated mammalian cells. See the specification at page 13, lines 3-6.

Adelman (2001, 2002, of record) taught that thoracic administration of antisense or siRNA expression vectors in mosquitoes allowed inhibition of DV replication in salivary glands. However, these teachings do not provide enablement for siRNA vector delivery and subsequent inhibition of DV replication in mammals due to the vast differences in size and complexity between the two classes of organisms. Further guidance as to how to achieve delivery of an siRNA vector to the appropriate target cells would be required in order to enable the scope of the claimed invention embracing delivery to cells in an mammal in vivo.

Guidance in the specification as to how to achieve delivery to DV target cells is general. For example, the specification at paragraph 50 indicates that the "vectors of the present invention can be administered to a subject by any route that results in delivery of the genetic material (e.g., polynucleotides) and transcription of the polynucleotides of the gene suppressor cassettes into siRNA molecules. The vectors of the present invention can be administered to a host "intravenously (I.V.), intramuscularly (I.M.), subcutaneously (S.C.), intradermally (I.D.), orally, intranasally, etc."

The specification at pages 29 and 30 teaches that dendritic cells (DC) are regarded as the targets for Dengue virus (DV) infection in mammals (citing Marovich (2001) and Wu (2000), of record)). Each of these papers shows that DV will infect DC in vitro, and provides evidence that DC cells present at a site of infection in vivo stained

positively for a DV antigen (see e.g. Marovich at paragraph bridging pages 222 and 223, and Fig 5 on pg 223). However, those of skill in the art appreciate that positive staining of phagocytic cells such as DC does not provide proof of infection of DC in vivo. Jessie et al (J. Inf. Dis. 189: 1411-1418, 2004) at page 1411, paragraph bridging columns 1 and 2, taught that "the mere presence of viral antigens within cells does not necessarily mean that the cells in question support viral replication, since antigens may represent phagocytized, killed virus or sequestered immune complexes in the process of being degraded." Jessie further stated that "[e]vidence from in vitro studies suggested that other cells (e.g., hepatocytes, B and T lymphocytes, endothelial cells, and fibroblasts) could be potential targets for virus infection and replication, but relatively little is known about the involvement of these cells in in vivo infections [12 citations omitted]." Wu indicated that the initial target cell for DV infection had not yet been identified (first sentence of introduction on page 816), and the work of Wu and Marovich does not provide such an identification in view of the later teachings of Jessie. In summary, at the time of the invention, in vivo targets for DV infection and replication had not yet been convincingly identified by those of skill in the art, and the specification fails to provide further evidence for identification of a target. Thus one of skill in the art relying on the teachings of the specification and the prior art would not know to which cells in a mammal an siRNA vector should be delivered.

It was also apparent from the teachings of the prior art that delivery of gene expression vectors in vivo, and obtaining appropriate expression therefrom, was

problematic. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art.

Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3).

Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

Rosenberg et al (Science 287 :1751, 2000) stated that "[a}t present the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical

trials a decade ago, gene therapy's leading proponents have given the field a positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." See first full paragraph.

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (pg. 581).

In summary, it is clear that in vivo gene delivery and expression is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date has fallen short of initial expectations due to inadequate delivery and expression systems.

The specification provides no working example of the claimed invention.

Because the target cells for DV infection were not known at the time of the invention, the specification provides only general guidance as to how to deliver the required expression vector, the state of the art regarding therapeutic gene expression in vivo shows a high level of unpredictability, and the specification lacks a working example, one of skill in the art could not deliver the required expression vector to the appropriate cells in a mammalian host to inhibit expression of Dengue Virus genes without undue experimentation.

Response to Arguments

Applicant's arguments filed 10/27/08 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 5 and 6 of the response. Applicant asserts that one of ordinary skill would expect that inhibition of expression of DV genes in a mammalian host animal can be achieved with the claimed methods cell correlates with inhibition of DV genes in a mammalian host, arguing that inhibition of DV expression in host cells in vitro correlates with the same process in vivo, and that the vector can be delivered to the appropriate cells in vivo. This is unpersuasive because it is not supported by evidence. As discussed above, DV inhibition by siRNA in vitro does not correlate with DV inhibition by siRNA in vivo because of art recognized difficulties in in vivo delivery and expression (see Verma (1997), Anderson (1998), Somia and Verma (2000), Rosenberg (2000), and Caplen (2003) above. The art of delivering gene expression cassettes to, and obtaining therapeutic expression within, specific target cells was highly unpredictable at the time of the invention even when the target cells were known. In this case, it is not known what is the in vivo target cell for DV replication (see Jessie (2004) and Wu (2000), above). Thus the unpredictability associates the invention is extreme.

Applicant disagrees that in vivo gene delivery is problematic and argues that there are numerous reports of successful gene delivery in vivo and several advanced clinical trials in progress. This is unpersuasive because it is unsupported by evidence. The examiner has provided documentary evidence prior to and after the time of filing

that shows that those of skill considered the in vivo delivery of gene expression vectors to be highly unpredictable due to targeting and expression problems. There have been gene therapy clinical trials ongoing since the mid-1990's, yet those of skill still find the field to be highly unpredictable due to problems with delivery and expression. Applicant argues that one could deliver to macrophage and dendritic cells using chitosan nanoparticles administered mucosally. This is unpersuasive because it is unclear for the reasons set forth above that macrophages and dendritic cells are target cells for DV infection in vivo. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635